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Previews

TCF7L2 and Diabetes: A Tale of Two Tissues, and of Two Species

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Human genetics is revealing ever more variants that influence propensity to common diseases, but progress in translating these discoveries into the biological mechanisms responsible for predisposition continues to lag behind. A recent paper in *Cell* (Boj et al., 2012) using rodent models to examine how diabetes-associated variants near *TCF7L2* perturb metabolic regulation provides surprising results.

Incomplete understanding of the physiological mechanisms involved in the development of type 2 diabetes (T2D) frustrates efforts to develop more effective strategies for prevention and treatment. Individuals with T2D characteristically display a constellation of metabolic abnormalities contributing to disturbed glucose regulation—including deficient secretion of insulin from the pancreatic β cells and reduced capacity of insulin to regulate metabolic processes in target tissues such as liver, fat, and muscle. However, the relationship between these apparently distinct derangements remains uncertain. Human genetics can help to disentangle such complex pathophysiological problems: for example, exploration, in nondiabetic subjects, of the metabolic effects of DNA variants shown to influence risk of T2D can illuminate critical, early steps in metabolic decompensation. For the 70 or so genetic regions now implicated in T2D predisposition, such studies have generally pointed toward the primacy of defects in insulin secretion. Evidence for a β cell mechanism has seemed particularly compelling for the T2D association signal which maps intronic to *TCF7L2*, the gene encoding the transcription factor TCF4. This signal has particular salience, as the variants concerned have a relatively large effect on T2D risk (a 30% increase per risk allele). However, a recent paper examining the metabolic effects of perturbing expression of the murine homolog, *Tcf7l2*, suggests a more complex picture (Boj et al., 2012).

Boj and colleagues (Boj et al., 2012) demonstrate that manipulation of islet *Tcf7L2* expression in adult mice (using the rat insulin promoter to restrict inducible knockdown of transcript expression to the insulin-secreting pancreatic β cells) has no demonstrable effects on glucose-stimulated insulin secretion. Instead, they report that, in both global knockout mice and in liver-specific inducible models, depletion of *Tcf7L2* is associated with hypoglycaemia and reduced hepatic glucose production. Conversely, overexpression of *Tcf7l2* in liver leads to enhanced hepatic glucose production and to glucose intolerance. The authors argue that *TCF7L2*-related disruption of β cell function is probably the indirect consequence of primary events in liver and elsewhere (see Figure 1).

On the face of it, these findings run counter to much of the existing evidence, from both humans and rodents. Physiological studies in nondiabetic human subjects have consistently shown that *TCF7L2* T2D risk alleles confer a metabolic picture dominated by reduced insulin secretion (Lyssenko et al., 2007). This is accompanied by a blunted response to incretins such as GLP-1, which have an important physiological role in boosting insulin secretion following meals. Diabetes-associated variation at *TCF7L2* has also been associated with altered pancreatic islet morphology (Le Bacquer et al., 2012) and, in human islet culture studies, with disruption of glucose-stimulated insulin secretion (Lyssenko et al., 2007; Rosengren et al., 2012; Le Bacquer et al., 2012). Molecular studies have revealed that the specific base change most strongly implicated in T2D risk in Europeans alters chromatin accessibility at a site involved in genomic regulation in islets, but not other tissues (Gaulton et al., 2010). These data indicate a clear relationship between *TCF7L2* variants implicated in T2D risk and altered islet function. Furthermore, they suggest that these effects are islet autonomous, rather than driven by changes in other tissues (see Figure 1).

The new data also appear at odds with other rodent studies. RNAi-based knockdown of *Tcf7L2* in rodent islets and β cell lines results in reduced insulin release, possibly due to defective insulin granule exocytosis (da Silva Xavier et al., 2009), and pancreas-specific *Tcf7l2* null mice display islet phenotypes—reduced insulin secretion, blunted incretin response, impaired β cell expansion—redolent of those seen in humans carrying *TCF7L2* risk alleles (da Silva Xavier et al., 2012). Unlike the inducible β cell-specific knockout model studied by Boj and colleagues (Boj et al., 2012), silencing of *Tcf7l2* expression in these pancreas-specific null mice involves other islet endocrine cells and pancreatic exocrine tissue, and extends through embryonic life as well as adulthood. Perhaps more extensive disruption of pancreatic development and/or loss of crosstalk between these different cell types is required for full expression of the islet phenotype.

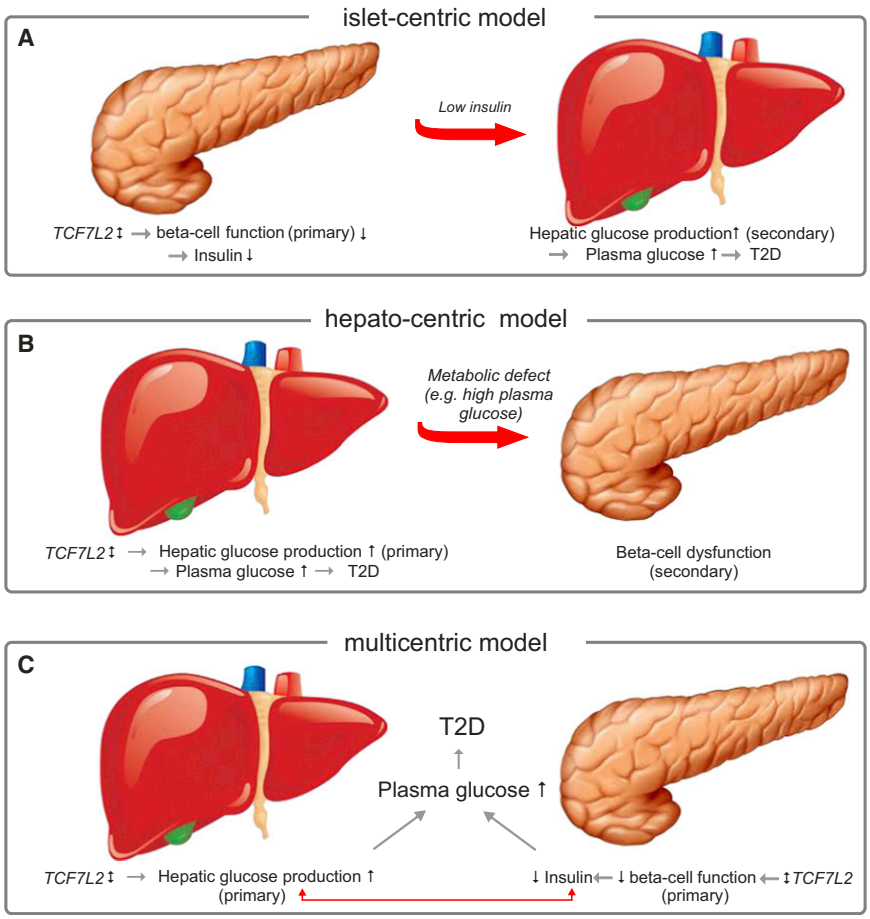

Figure 1. Alternative Models for Mechanisms Linking *TCF7L2* to T2D Pathogenesis

(A) Islet-centric model: most of the evidence to date has indicated that the critical feature associated with sequence or expression changes in and around *TCF7L2* is one of pancreatic islet dysfunction, with other changes likely secondary.

(B) Hepatocentric model: the recent paper by Boj and colleagues (Boj et al., 2012) suggests that the major changes in metabolic regulation following disruption of *TCF7L2* expression are hepatic rather than pancreatic.

(C) Multicentric model: the overall pattern of findings is consistent with independent pancreatic and hepatic contributions to T2D pathogenesis.

Alternatively, it may simply be that variation in phenotype reflects subtle differences in mouse strains or environment: similar divergence of phenotypic expression has been observed in murine studies of other T2D risk loci.

What other explanations are consistent with this body of data? First, it is entirely possible that perturbation of *TCF7L2* expression influences homeostatic processes in both pancreas and liver (see Figure 1). While human physiological studies have highlighted deficient insulin secretion, a concomitant increase in hepatic glucose output has been reported (Lyssenko et al., 2007). If the T2D risk variants near *TCF7L2* have independent effects involving multiple tissues, models of tissue-specific perturbation, however powerful in other settings, may fail to do justice to the complex temporal and spatial interplay that is central to maintenance of glucose homeostasis.

Second, and as some of the studies above demonstrate, there is remarkably little consistency regarding the directional relationship between *TCF7L2* expression and glucose intolerance. While some rodent studies have demonstrated that reduced *Tcf7l2* expression results in diabetes (da Silva Xavier et al., 2009), others have found the opposite (Savic et al., 2011). In humans, limited islet expression data suggest that individuals carrying T2D risk alleles at *TCF7L2*, and those with T2D itself, have increased *TCF7L2* transcript levels (Lyssenko et al., 2007). However, in human islets, impaired glucose-stimulated insulin secretion has been reported following both T*CF7L2* suppression (Shu et al., 2008) and overexpression (Lyssenko et al., 2007). These divergent effects raise concerns about the biological relevance of perturbing total transcript levels. T2D risk variants have been proposed to influence *TCF7L2* splicing patterns, and it may be the ratio of functionally distinct mRNA isoforms, rather than the overall level of expression, which defines their phenotypic consequences (Hansson et al., 2010). More complex, ''humanized'' models will be required to explore this.

Finally, it is worth emphasizing that we have only circumstantial evidence that these T2D risk variants mediate their metabolic effects through *TCF7L2*. Experimental manipulation of *TCF7L2* will be of limited value if other regional transcripts regulated by these variants contribute the major diabetogenic impact. This is a question that may be settled by resequencing studies: identification of human subjects who carry alleles disrupting the *TCF7L2* coding sequence (assuming these are compatible with life) would enable direct exploration of the phenotypic consequences of isolated *TCF7L2* dysfunction.

These intriguing findings provide a timely reminder of the difficulties which attend the generation of robust biological inference from the (mostly noncoding, mostly modest effect) risk variants that have recently been implicated in common disease. In the 7 years since the *TCF7L2* signal was discovered, over 60 additional loci have been shown to influence T2D predisposition. However, for most, as with *TCF7L2*, the processes that link this variation to diabetes risk remain unclear. Novel approaches that address the evident complexity of these systems will be key if the field is to make progress in understanding and combating T2D and other complex diseases.

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The Hunger Games: p53 Regulates Metabolism upon Serine Starvation

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Cancer cells reprogram their metabolism to support a high proliferative rate. A new study shows that, upon serine starvation, the tumor suppressor p53 activates p21 to shift metabolic flux from purine biosynthesis to glutathione production, which enhances cellular proliferation and viability by combating ROS (Maddocks et al., 2013).

Cancer cells have designated hallmarks differentiating them from nonneoplastic cells: genomic instability, resistance to cell death, uncontrolled proliferation, and metabolic reprogramming, to name a few (Hanahan and Weinberg, 2011). The latter has been gaining increased attention. Cancer cells can reprogram their metabolism by shifting from oxidative phosphorylation to aerobic glycolysis, which defines the Warburg effect (Ward and Thompson, 2012). Although aerobic glycolysis produces far less ATP, an increase in macromolecule production along with an avoidance of heightened ROS accumulation from oxidative phosphorylation have been postulated for this metabolic reprogramming (Vander Heiden et al., 2009). Recent advances have shown that several features of altered metabolism can be dictated by specific oncogenes or tumor suppressors (Ward and Thompson, 2012). Classically known for inhibiting malignant transformation by regulating DNA repair, cell-cycle arrest, and apoptosis, the tumor suppressor p53 also upregulates metabolic targets to inhibit tumorigenesis (Li et al., 2012). Further, recent evidence suggests that p53 may also regulate glycolysis and oxidative phosphorylation in a cell- and context-specific manner (Gottlieb and Vousden, 2010). In an elegant study conducted by Karen Vousden's group, Maddocks et al. demonstrate that serine starvation activates p53 to reprogram metabolism and increase cancer cell survival (Maddocks et al., 2013).

Reprogramming metabolic flux makes cancer cells increasingly dependent on specific metabolites; de novo serine synthesis has been recently shown to be crucial for cancer cell proliferation and survival (Chaneton et al., 2012; Locasale et al., 2011). Under serine starvation conditions, Maddocks et al. initially observed a decrease in cell proliferation and survival that was more pronounced in p53-deficient colon cancer cells compared to isogenic p53 wild-type cells. When these tumor cells were xenografted in nude mice fed a diet lacking serine, p53-deficient tumors exhibited a stronger decrease in tumor volume than wild-type tumors (Maddocks et al., 2013). It has recently been shown that serine deprivation forces cancer cells into a "fuel-efficient mode" where the glycolytic intermediate 3-phosphoglycerate (3-PG) shuttles into the Serine Synthesis Pathway (SSP), while pyruvate enters the TCA cycle, thereby increasing oxidative phosphorylation and limiting the production of lactate (Chaneton et al., 2012). Maddocks et al. found that SSP enzymes were similarly activated upon serine starvation, independent of p53 status, ruling out a defective SSP and subsequent improper de novo serine synthesis as a potential candidate for the observed proliferative failure in $p53^{-/-}$ cells (Maddocks et al., 2013). Using oxygen consumption as a read-out for oxidative